UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,711	05/08/2002	Audrey Goddard	P3230R1C001-168	8521

30313 7590 06/14/2005

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,711	GODDARD ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,11-14 and 16-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,11-14 and 16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

pd

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/05 has been entered.

Response to Arguments

The rejection of claims under 35 USC 101 is withdrawn upon further reconsideration. However, the claims remain rejected under 35 USC 112, first paragraph, for lacking enablement.

The rejections of claims 1-3, 7-10 and 15 are moot in view of the cancellation of the claim.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14, 15, 21-25 and dependent claim 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 15 and 21-25 are indefinite for reciting "at least about" X nucleotides in length. It is unclear what range is intended by "at least about". At least 10 nucleotides means 10 or more. It is not clear if "at least about" means, for example, at least 10 or can be less than (about) 10.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6, 11-14, 16-20 remain and new claims 21-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons set forth in the previous Office action, including those which address the new and amended claims:

New claims 21-31 are drawn to a nucleic acid at least 95% identical to SEQ ID NO:77 or the coding region thereof. These new claims have the same structural identity requirements as, for example, claim 4, with the exception that they lack a functional limitation. Therefore, they are not enabled for the reasons of record and as discussed below. The amendments to claims 4-6, 11-14 and 16-17 provide limitations which make the claims more structurally narrow than before, but do not overcome the lack of enablement of the claims for reasons of record.

Applicants' response to the rejection under 101 is partly applicable to the rejection under 35 USC 112, first paragraph (see Applicants' response on p. 27). Those arguments which still pertain to the enablement rejection will be addressed here.

First, it must be stated that the asserted utility for the nucleic acid as a tumor marker for stomach and lung tumor is accepted. However, the use is not enabled as will be discussed here. Also, those arguments relating to the enablement of the expressed encoded polypeptide are moot because the claims no longer refer to the polypeptide in this application.

Applicants argue on page 9 that *In re Brana* states that "Usefulness in patent law... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to administer to humans." The argument has been fully considered, but is not persuasive. While *Brana* did deal with a rejection under 35 USC 112, first paragraph, the rejection was direct toward utility—specific, substantial

and credible use—instead of enablement. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement, one must know how to use the invention without undue experimentation. In the instant situation, Applicants claim a nucleic acid which is at least 95% identical to SEQ ID NO:77 or the coding region (ORF) thereof or hybridizes under recited conditions to SEQ ID NO:77 and is at least (about) 20 nucleotides in length.

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention is not enabled. As to the nature of the invention, it is a nucleic acid with no other known specific association than that asserted by Applicants of underexpression in stomach and lung tumors. It does not encode a protein with a recognized/characterized physiological/biochemical property. The non-identical nucleic acids (those which hybridize or are not 100% identical to SEQ ID NO:77 or its ORF) have not been shown to be underexpressed in any tumors or exists in nature. As to the state of the prior art, other nucleic acids usable for tumor markers had been identified, though none identified as such were identical or highly similar to SEQ ID NO:77. Therefore, the connection of SEQ ID NO:77 to tumors was not known. While the skill in the art for differential screening has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, it was not routine to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid. There are no working examples of nucleic acids at least 95% identical to or hybridizing under the recited conditions which are underexpressed in stomach or lung tumors other than SEQ ID NO:77 itself. The breadth of the claims is broad, encompassing structural variation and, in the case of claims 14, 16 and 19-31, no functional limitation. There is very little guidance or direction about using the claimed nucleic acid of SEQ ID NO:77 except the information that it is underexpressed in stomach and lung tumors. As discussed in previous Office actions, the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor

tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

On page 10, Applicants cite *Fujikawa v. Wattanasin* and *Cross* cases, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo*. The argument has been fully considered, but is not persuasive. As stated in the previous Office action mailed 3/4/05, "At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure ...to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: whether differences in expression of PRO1357 were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention."

Applicants argue (pp. 12 and 14-15) that the Declaration of Grimaldi demonstrates at least a two-fold difference in expression between normal and tumor tissues and the usefulness of the claimed nucleic acid as a diagnostic tool for determining the presence or absence of a tumor. The argument has been fully considered, but is not persuasive. This conclusory statement does not enable the invention because it does not fill important gaps in the disclosure needed to enable using the invention without significant further experimentation, such as expression level range for normal and tumor tissues, specific types of stomach or lung tumors detectable, and probability of detection for any particular stomach or lung tumor type (*e.g.*, whether one would reasonably expect underexpression in 10/10 or 1/20 tumors tested). Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues, this does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says (¶5) that "Data from a pooled sample are more likely to be accurate that data from a single individual." This bags the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected

cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of stomach or lung tissue that can used, and other questions, the specification has not provided the invention in an enabling form. Therefore, even accepting Dr. Grimaldi's opinion (see first paragraph of p. 16 of response), the declaration is insufficient to overcome the rejection of the claims under 35 USC 112, first paragraph, for the reasons discussed above.

Applicants argue (p. 22) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) are not surprising and provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant.

Applicants argue (p. 23) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enabled that particular gene to be used diagnostically. In this case, the prior art provides no information about the use of the gene and the specification does not provide an enabling disclosure for use of the PRO1357 nucleic acid as a diagnostic tool for stomach or lung tumors based on differential expression for the reasons discussed above and in previous Office actions. As to the claims drawn to nucleic acids not identical to SEQ ID NO:77 or its ORF, even if SEQ ID NO:77 were enabled for a diagnostic tool, nucleic acids not identical would not be because it was not routine or expected for the skilled artisan to use a probe not identical to the target nucleic acid sequence for detection of the target nucleic acid when the sequence of the target nucleic acid was known. Also, with unknown relative differences, it is unpredictable how different a polynucleotide probe could be from SEQ ID NO:77 and be used for differential expression.

Claims 4, 5 and 17-20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action

Applicants argue (p. 29-31) that if there are sufficient identifying characteristics, *e.g.*, functional characteristic coupled to a structure, or hybridization conditions providing a limitation for claimed nucleic acids, that is sufficient for written description. In the instant application the function is expression in normal stomach and lung or higher expression there than in stomach or lung tumor. The argument has been fully considered, but is not persuasive. The point is not the ability to hybridize. The point is that **not** all hybridizing nucleic acids and **not** all nucleic acids 99% identical to SEQ ID NO:77 are included. Only those that naturally occur in stomach or lung are included. Applicants have disclosed no concept of which nucleic acid(s) which is not identical to SEQ ID NO:77 (or the coding region) are present in stomach or lung. The specification does not convey to one of skill in the art, including recombinant DNA/protein technology, that the inventors were in possession of these non-identical naturally occurring nucleic acids. The specification does not provide information so the skilled artisan could readily envision such nucleic acids. For these reasons and those previously of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

Claims 4-6, 11-14 and 16-20 remain and new claims 21-31 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/16318 or WO 00/12708 for the reasons set forth in the previous Office action.

Applicants argue that the instant application receives an effective filing date of 08/24/00 because the data of Example 18 was disclosed therein. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application likewise do not meet those

requirements, the instant application does not receive benefit of priority to earlier filed applications. Even though SEQ ID NO:77 and 78 and the expression information of Table 18 were previously disclosed, enablement thereof has not been established as discussed above.

Claims 14, 16, 21-25 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession BG529820.

GenBank Accession BG529820 teaches a nucleic acid that is more than 250 base pairs long and is 97.6% identical over its entire length so it would hybridize to SEQ ID NO:77 under the conditions listed in claim 14 and is, therefore, suitable for a probe.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

June 9, 2005